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Pin-pointing phosphorylation-dependent Pin1 binding to a cytoskeletal protein altered in Alzheimer's Disease using structural mass spectrometry

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Abnormal protein phosphorylation is a fundamental trigger in the pathogenesis of Alzheimer's Disease, leading to the formation of neurofibrillary tangles. Thus, molecular determination of the critical factors in controlling phosphorylation is in high demand. Pin1, a cis-trans prolyl isomerase has recently been implicated in Alzheimer's Disease progression. Moreover, Pin1 specifically targets phosphoproteins, regulating their function. Here, we utilise a combination of native MS and top-down MS to reveal a novel interaction between Pin1 and the Collapsin Response Mediator Protein-2 (CRMP2); a protein found hyperphosphorylated alongside tau within neurofibrillary tangles. Using native mass spectrometry, we show that Pin1 binds specifically to the disordered C-terminus of CRMP2 in a phosphorylation-dependent manner. Hydrogen-deuterium exchange mass spectrometry experiments further localised this binding site to the WW-domain of Pin1. Together, the data highlights how mass spectrometry has been utilised to provide novel insight into the regulatory role of Pin1 in a disease-relevant context.

User consent

yes

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